DETAILED ACTION

Status of the Application

Receipt of the Response after Non-Final Office Action, the Amendment and Applicant's Arguments/Remarks, all filed 03/05/08 and the Information Disclosure Statement (IDS) filed 11/13/07 is acknowledged.

Claims 1-56 are pending in this action. Claims 1, 15, 16, 17, 18, 27 and 37 have been amended. New claims 39-56 have been added. Claims 1-7, 9-17, 27-33, 35, 36 and 39-56 remain rejected. Claims 18-26, 37 and 38 are allowed. Claims 8 and 34 are objected to.

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Claim Objections

Claims 39, 41, 43, 45, 47, 49, 51, 53 and 55 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims recite the limitation "wherein the active agent is selected from the group consisting of hydrocodone, a non-opioid drug, their mixtures and pharmaceutically acceptable salts thereof". The limitation of 'selected from the group consisting of hydrocodone and pharmaceutically acceptable salts thereof' fails to further limit the independent claims from which they depend from. Note that the independent claims (i.e., 1, 15, 16) already contain the recitation of "hydrocodone or a pharmaceutically acceptable salt thereof".

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New claims 39-56 are indefinite because the limitation reciting "wherein the active agent is selected from the group consisting of hydrocodone, a non-opioid drug, their mixtures and pharmaceutically acceptable salts thereof" renders the claims confusing and unclear. Claim 1 for instance, on which claim 39 depends, already requires the use of either "hydrocodone or a pharmaceutically acceptable salt thereof". However, the newly added claims (i.e., claim 39) recites a Markush group giving the option of having a hydrocodone and pharmaceutically acceptable salts thereof, but claim 1 already requires a hydrocodone or pharmaceutically acceptable salt thereof. It appears that Applicant intended to provide limitations drawn to "further comprising a non-opioid drug…" Clarification is requested.

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Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7, 9-17 and 39-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo (WO 99/32120).

Palermo (WO '120) teaches an oral dosage form of an opioid analgesic, comprising an analgesically effective amount of an opioid agonist together with an opioid antagonist, the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist (see p. 6, lines 1-18).

In certain preferred embodiments, the opioid agonist is hydrocodone, hydromorphone, oxycodone, morphine or pharmaceutically acceptable salts thereof (p. 7, lines 5-6). Suitable opioid antagonists disclosed include naltrexone, naloxone, nalmephene, cyclazocine and levallorphan. A most preferred antagonist is naltrexone (p. 11, lines 14-19); (p. 13, lines 14-31). In certain preferred embodiments of the method, the opioid agonist and the opioid antagonist are combined in a ratio of opioid antagonist to opioid agonist which is analgesically effective when the combination is administered orally, but which is aversive in a physically dependent subject (p. 7, lines 7-15). In embodiments where the opioid is hydrocodone and the antagonist is naltrexone, the ratio of naltrexone to hydrocodone is preferably from about 0.03-0.27:1 by weight (p. 7, lines 15-26).

Palermo teaches that the dosage forms of the invention may be liquids, tablets, multiparticulates, dispersible powders or granules, hard or soft capsules, lozenges, aqueous or oily suspensions, emulsions, syrups, elixirs, microparticles, buccal tablets, etc. (p. 7, lines 27-31); (p. 8, line 29 – p. 9, line 1). In certain preferred embodiments, the oral dosage forms are sustained release formulations. This may be accomplished via the incorporation of a sustained release carrier into a matrix containing the opioid agonist and opioid antagonist; or via a

sustained release coating of a matrix containing the opioid agonist and opioid antagonist, where the sustained release coating contains at least a portion of the sustained release carrier included in the dosage form (p. 8, lines 1-9); (p. 20, lines 16-21).

With regards to ratios, Palermo teaches that the combinations of opioid antagonists/opioid agonists which are orally administered in ratios which are equivalent to the ratio of e.g., naltrexone to hydrocodone set forth are considered to be within the scope of the invention. For example, in some embodiments, naloxone is utilized as the opioid antagonist, the amount of naloxone included in the dosage form being large enough to provide an equiantagonistic effect as if naltrexone were included in the combination (p. 19-31). This demonstrates bioequivalency of the dosage forms.

Palermo teaches that the dosage forms may be coated with one or more materials suitable for the regulation of release or the protection of the formulation. The coatings are provided to permit either pH-dependent or pH-independent release (p.21, lines 18-29).

In preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (p. 22, lines 6-14).

Suitable and preferred alkylcellulose polymers taught include ethylcellulose (p. 22, lines 19-25). Acrylic polymers are also disclosed and include acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid) and the like (p. 23, line 10 – p. 24, line 22); (p. 29, lines 7-18). Plasticizers can also be included in the composition (p. 24, line 24 – p. 25, line 20). A process for preparing coated beads is disclosed at p. 25, line 21 – p. 28, line 8.

Matrix bead formulations are disclosed at page 28. Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials and any pharmaceutically acceptable hydrophobic material or hydrophilic material, which is capable of imparting, controlled release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in this invention (p. 28, lines 19-30).

With regards to amounts of hydrophobic material claimed, the Examiner notes that suitable or effective amounts can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results, as these are variable parameters attainable within the art. Moreover, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The Palermo reference explicitly recognizes and teaches oral dosage forms comprising opioid agonists in combination with opioid antagonists, whereby the dosage forms are effective for the substantial reduction of pain. Given the teachings of Palermo, the instant invention, when taken as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

This rejection has been maintained and applied to newly added claims 39-48. Palermo teaches an oral dosage form of an opioid analgesic, whereby the active agent can be hydrocodone. See p. 7, lines 5-6. Palermo also teaches formulations that include the use of acetaminophen and aspirin. See page 16, lines 5-17.

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Claims 27-33, 35, 36 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo (WO 99/32120), as applied to claims 1-26 above and further in view of Elger *et al.* (U.S. Pat. No. 4,844,907).

Palermo (WO '120) teaches an oral dosage form of an opioid analgesic, comprising an analgesically effective amount of an opioid agonist together with an opioid antagonist, the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist (see p. 6, lines 1-18). In certain preferred embodiments, the opioid agonist is hydrocodone, hydromorphone, oxycodone, morphine or pharmaceutically acceptable salts thereof (p. 7, lines 5-6).

Palermo does not explicitly teach *layered* dosage forms.

Elger *et al.* ('907) teach a pharmaceutical composition for the treatment of pain comprising a narcotic analgesic and a non-steroidal anti-inflammatory drug, whereby the composition is in the form of a multi-phase, layered tablet, especially bi-layered tablet (see reference column 1, line 1 – col. 2, line 3) and Abstract.

Suitable narcotic analgesics disclosed include hydrocodone, morphine and codeine (see Table at column 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the layered dosage forms of Elger *et al.* within the formulations of Palermo. One of ordinary skill in the art would do so because Elger *et al.* teach layered pharmaceutical compositions comprising narcotic analgesics and teach that the layered dosage

forms (*i.e.*, bi-layered dosage forms) provide for separation of different drugs or phases. The expected result would be an improved multi-layered dosage formulation for the effective treatment of pain.

This rejection has been maintained and applied to newly added claims 49-52. Palermo teaches an oral dosage form of an opioid analgesic, whereby the active agent can be hydrocodone. See p. 7, lines 5-6. Palermo also teaches formulations that include the use of acetaminophen and aspirin. See page 16, lines 5-17. Additionally, Elger teach a narcotic analgesic and a non-steroidal anti-inflammatory drug. See column 1, line 1 – col. 2, line 3.

Response to Arguments

Applicant's arguments filed 03/05/08 have been fully considered and were found to be partially persuasive.

- **Rejection under 35 U.S.C. §103(a) over Palermo (WO 99/32120):**

Applicant argued, "The Palermo publication does not disclose any specific pharmacokinetic values (i.e., C_{24} and C_{max}) for the dosage forms described therein. The Palermo publication does not describe any in vivo dissolution data. With regard to new claims 39, 41, 43, 45 and 47, the dosage form in accordance with the Palermo publication would necessarily include an opioid antagonist."

Applicant's arguments have been thoroughly considered and were found persuasive with respect to claims 8, 18-26, 34, 37 and 38 which provide for specific release rates of hydrocodone. With regards to the remaining claims, admittedly, while the Palermo publication does not teach the pharmacokinetic values (i.e., C_{24} and C_{max}) for the dosage forms instantly claimed, the

publication nonetheless is sufficient for the teachings of providing for the use of the same ingredients for use in the same field of endeavor as that of the Applicant's dosage form. The C_{24} and C_{max} ratios provided by Applicant do not establish a patentable distinction over the explicit reference teachings of Palermo since the formulations of Palermo would also be capable of providing for beneficial results, absent a showing of evidence to the contrary. Moreover, the determination of suitable or effective ratios is within the level of one of ordinary skill in the art, obtained through routine or manipulative experimentation to obtain optimal results. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to Applicant's argument that "The Palermo publication would necessarily include an opioid antagonist", this argument was not rendered persuasive. The instant claims utilize "comprising" claim language and thus do not exclude the additional opioid antagonists taught by Palermo. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended.").

- **Rejection under 35 U.S.C. §103(a) over Palermo (WO 99/32120) in view of Elger et al. (USPN 4,844,907):**

Applicant argued, "The combination of the cited references does not describe an osmotic dosage form as recited in independent claims 27, 36, 37 and 38. The combination of references does not render obvious the specific C_{24}/C_{max} ratios recited in the present claims. With regard to new claims 49, 51, 53 and 55, the dosage form in accordance with the Palermo publication would necessarily include an opioid antagonist."

These arguments were found persuasive with regards to claims 37 and 38. Claims 37 and 38 are indicated as being allowable. The remaining claims remain rejected over the combination of the reference teachings. The secondary reference of Elger amply remedies the deficiency of the Palermo publication by their teaching of layered formulations that comprise opioid agonists, i.e., hydrocodone. See Elger - Table at column 2. With regards to the instant ratios, while the instant ratios are not suggested, it remains the position of the Examiner that the instant ratios do not provide for any unexpected results, which would render a patentable distinction over the combination of the applied art. The formulations of the art would also be fully capable of providing for beneficial results, absent a showing of evidence to the contrary.

With regards to Applicant's argument that "The Palermo publication would necessarily include an opioid antagonist", this argument was not rendered persuasive. The instant claims utilize open-ended "comprising" claim language and thus permit the presence of additional agents or components asides from those instantly recited; the additional agents being the opioid antagonists taught by Palermo. The instant claims are not limited to a single active agent, i.e., hydrocodone.

The rejections of record have been maintained.

Allowable Subject Matter

Claims 18-26, 37 and 38 are allowed.

Claims 8 and 34 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 53-56 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley, can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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/Humera N. Sheikh/

Primary Examiner, Art Unit 1618

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